Counsyl Autosomal Dominant Disease Classification criteria (2015)

Known Deleterious (KD)*	1 of A[#] and C and H **OR** 1 of B and 1 of G and H	A	Truncating variants (nonsense, fs) that result in a premature termination codon that is 5' of the theoretical NMD boundary
			Large genomic duplications that result in a frame shift before the NMD boundary
			Frame shift that disrupts a known active site (nucleotide or substrate binding site) or other known domain known to be essential for protein function
			Amino acid change is the same as a KD unless the mechanism of pathogenicity is altered splicing
			Large genomic deletions
			Canonical splice variant AND *in silico* tools predict strong effects on splicing
		B	Significant segregation with disease (LOD score >3.0)
			Significant association in cases using ethnically matched controls
		C	At least 2 cases with phenotype consistent with disease
Likely Deleterious (LD)*	1 of A[#] and D and H OR E and D and H **OR** 1 of F and 2 of G and H	D	At least 1 case with phenotype consistent with disease
		E	In-frame deletion/duplication of a single exon not known to be important for protein function
		F	Suggestive association in cases using ethnically matched controls
			Suggestive segregation with disease (LOD= 1.5-3.0)
		G	At least 2 independent functional assays demonstrating deficient protein function
			In a known mutational hotspot (well-documented in the literature) critical for protein function or occurs in the same codon as a KD (weighted stronger if variant aa is similar to KD)
			Validated in silico algorithm predicts deleterious effects
			Additional evidence of pathogenicity

		H	Variant is absent or rare in population databases (Ex: ESP)
Predicted Deleterious (PD)*	1 of A[#] and H and I **OR** E and H and I	I	Not reported in cases
Variant of Uncertain Significance (VUS)		J	Insufficient or conflicting data
Likely Benign /Predicted Benign (LB/PB)	1 of K	K	Allele frequency ≥ 0.5% in population databases (Ex: ESP) and there are no reported cases
			Non-canonical splice and silent variants with no effects on splicing demonstrated by laboratory assay
			Alteration is observed in trans with a KD in at least 2 individuals with disease (for genes with a clear bi-allelic phenotype)
			Silent variant with poor conservation and no predicted splicing effects (Predicted benign)
Known Benign (KB)		L	Allele frequency ≥1% (95% CI > 0.01) in at least 1 population and the variant is not a founder mutation

[#]Only applies to genes for which loss of function is a known disease mechanism

*Variants associated with diseases other than those on the testing panel are given the classification of Variant of Unknown Significance.

When available, classifications provided by expert panels and/or multifactorial analyses of large datasets are utilized (Ex: InSight classifications for Lynch Syndrome genes and IARC classifications for BRCA1/2).